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## Granulocytopenia : review with special considerations to etiology, pathology and the relationship of the sulfonamide derivatives

Harold H. Stowe  
*University of Nebraska Medical Center*

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GRANULOCYTOPENIA  
A REVIEW  
WITH  
SPECIAL CONSIDERATION  
TO  
ETIOLOGY, PATHOLOGY AND  
THE RELATIONSHIP OF THE SULFON-  
AMIDE DERIVATIVES

BY  
Harold Robert Stowe

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## INTRODUCTION

Few syndromes in medicine have as bizarre and often as catastrophic features as Granulocytopenia. Confined to no sex or age group, it hits rich and poor alike. Known for only a short time, it assumes increasing importance as medicine enters its chemotherapeutic age. Even now, forty years after the first recorded observations on the disease, there is considerable confusion regarding it. Some investigators feel that they deal with a group of diseases rather than a single disease entity. This paper, arranged in more or less text book fashion, represents a review of the established observations with particular emphasis on the later literature and the relation of the syndrome to the drugs of the para-amino-benzene-sulfonamide series.

## DEFINITION

Granulocytopenia is a disturbance of the hematopoietic system caused by various known and unknown factors. It is a syndrome rather than a disease and is characterized by an acute febrile course with high mortality, ulcerative lesions of the mucus membranes, particularly in the oral cavity, and a striking leukopenia, in which there is a complete or almost complete absence of cells of the granulocytic variety. The bone marrow may be normal, hypoplastic or hyperplastic.

## HISTORY

Blood counts have been made in large hospitals for the past fifty years. Never the less, the disease was reported with such extreme rarity prior to 1922 that we usually date it from the observations of Schultz in that year.

Pepper (65), in his history of malignant neutropenia, stated that the disease was mentioned in laryngologic works of sixty years ago as "putrid sore throat", and "gangrenous angina", and he said that Mackenzie, in his manual of diseases of the nose and throat, credited Gubler, in 1857 and Trousseau, in 1865 with having distinguished the disease from diphtheria. The first case reported in this country was that of Brown (9) in 1902. This was reported as acute primary, infectious pharyngitis with extreme leukopenia and terminated fatally. Turck (88) reported one case in 1907. Leale (53) in 1910, reported a case in a male child two and one half years old under the title "Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture."

Baldrige and Needles (62), In 1910, reported a case and pointed out that in former years it was either overlooked because the blood was not examined or was interpreted as a symptom of bone marrow ~~ex~~haustion, aplastic anemia, or aleukemic leukemia.

Schultz(84) in 1922 described fully four cases in middle aged women characterized by severe leukopenia, a decrease or absence of granular cells in the blood, gangrenous throat lesions and a rapid, septic course with death in from two to seven days. He noted the

normal red count, the frequent jaundice, the paucity of myeloid cells found in the bone marrow at autopsy. Since this description many similar cases have been reported, particularly from Germany and America. Many of the cases have departed in one or more particulars from this "Schultz" type. Our concept of the condition has changed gradually as it has become apparent that a large number of bacterial, toxic, chemical and physical agents can produce a very similar picture. The group of cases designated "idiopathic" is becoming steadily smaller as definite etiological agents are discovered.

#### NOMENCLATURE

Since the description of Werner Schultz in 1922, many attempts to standardize the nomenclature have been made. Schultz proposed the term "Agranulocytosis". This term, while brief, is ambiguous. By "agranulocytes" are meant those neutrophils without granulations which are seen in blood smears from cases of leukemia. The term "Agranulocytosis" suggests an increase in these atypical neutrophils, quite the opposite from the impression desired.

The name "Agranulocytic Angina", perhaps in greater use than any other, was proposed by Friedemann (28) who was impressed by the usual localization of lesions in the throat. This term has the same intrinsic ambiguity regarding the granulocytes as the first one mentioned and is doubly undesirable in the light of later day

knowledge that cases do exist without angina.

Schilling (82), suggested the term "malignant Neutropenia" which contains no ambiguities but does not recognize that there are also benign and recurrent forms.

Rosenthal (76) in his classification divided neutropenia into malignant (fatal) and benign (recovered) cases.

Many other terms have been suggested, such as agranulosis, mucositis necroticans agranulocytica, monocytic angina, sepsis with granulopenia, idiopathic neutropenia and pernicious leukopenia.

Beck (4) has suggested a rather adequate classification into 1. primary benign and primary malignant neutropenia in which the etiology is unknown; 2. secondary benign and secondary malignant neutropenia, the cases in which the etiologic agents are evident or in which one is dealing with well recognized clinical entities.

For a simple term covering the syndrome in a general way I should like to propose the name "Granulocytopenia". This is a trifle more descriptive than the term "Neutropenia" and conveys the idea that there is a shortage of cells of the granulocytic series.

#### ETIOLOGY

During the short time that we have recognized the syndrome of granulocytopenia our conception of it has changed tremendously. Werner Schultz advanced no theory

as to the cause of it. He remarked that it seemed to occur in women and was invariably fatal. (Since that time numerous cases have occurred in males and numerous cases have recovered.)

Hueper (33) found a ratio of three and one half women to one man, or 77.5 % in women. Roberts and Kracke (73) presented a table compiled from 8,000 leukocyte and differential counts which showed this trend in chronic cases (56 % being in females). The majority of cases seem to occur in the fourth decade of life. Cases have occurred in children, in young adults and in very old people, but these are more rare. The two countries which seem to have the greatest incidence are Germany and the United States.

Gordon (29) in his article on the etiology and treatment of granulocytopenia has given a classification of the various <sup>factors</sup> which have at one time or another been incriminated in the production of the syndrome.

A. Unknown- the malignant neutropenia of Schultz.

B. Chemicals and drugs - benzol, hydrocarbon, trinitro-toluene, arsenobenzol, bismuth, bismarsen, amidopyrine, barbital, dinitrophenone etc.

c. Bacteria - streptococci of all types, staphylococci ( aureus and albus), Vincents' spirillum and the fusiform bacillus, pneumococcus, gram negative and gram positive cocci, gram negative and gram positive bacilli, bacillus coli, bacillus pyocyaneus, bacillus subtilis, bacillus diptheriae, the meningococcus and the gas gangrene bacillus.



D. Malignant neutropenia has developed in people under treatment for; cholecystitis, cardiac disease, arthritis, amebic and ulcerative colitis, furunculosis, syphilis, tuberculosis and cancer.

E. Allergy, particularly asthma, has been reported to be one of the causes of malignant neutropenia.

F. A congenital condition of the bone marrow has been demonstrated and a maturation arrest described by some authorities as a cause.

G. Biologically, it has followed the use of prophylactic typhoid serum and diphtheria anti-toxin.

H. Physically it has followed the use of x-ray therapy. Extraction of teeth and fractures of bone have been described as etiological factors.

I. The menses and pregnancy have been described as etiological factors.

(Gordon does not feel that drugs are the predominant etiological factor. In his series of 59 cases only one had taken medicines of the benzene series. This view is concurred in by T.H. Boughten of Akron, Ohio, who states that in the rubber factories where benzene is in general use among the workers he has seen a great many cases of benzene poisoning, yet in spite of constant watchfulness has seen only two cases of agranulocytosis, neither of the workers having been exposed to any form of industrial poisoning.) (54)

On the opposite side of the fence may be balanced the classic work of Kracke and his associates, (41-46)

(63) who in 1934 declared flatfootedly that "acute fulminant granulopenia and other types as well are caused for the most part by the administration of easily oxidizable benzene ring drugs!!" Others of their conclusions were: not the benzene nucleus itself, but an oxidizable end product of it (quinone or catechol) is at fault. This was proven by injecting rabbits with benzene, inducing granulopenia and recovering catechol from the bone marrow. They also oxidized amidopyrine and phenacetine, two of the drugs more commonly associated with granulocytopenia, and proved by chemical reactions and spectrum analysis that one of the end products was quinone.

In an analysis of 1314 cases, four drugs were incriminated by Kracke and associates: gold salts, arsphenamine, amidopyrine and phenacetin. It was pointed out that these all have certain structures in common, the benzene grouping with an attached amino radical. Straight chain barbiturates they did not incriminate but those with the benzene nucleus were found to be associated with the syndrome.

Kracke and associates also pointed out the quite interesting and significant fact that physicians, nurses, pharmacists and those in contact with benzene drugs have a far greater incidence as a class.

In an address delivered before the 1940 meeting of the Omaha Midwest Clinical Society, Dr. Kracke listed several other drugs which have been found at times to be associated with the syndrome. These include

dinitrophenol, used to reduce weight, gold salts, used in arthritis, organic arsenical compounds, used in syphilis therapy, and the sulfanilamide derivatives.

The flaw, of course, in the theory of the causation of the syndrome by drugs alone is that their action can not be predicted and it is impossible to effect a reduction of the human white count by experimental giving of the drugs. Apparently some peculiar set of circumstances must be present in the body economy where the neutropenic state can be induced by the coal tar products and others. Parker and Kracke (63) have recently suggested that the reduced form of glutathione plays an important part in the regulation of bone marrow activity. They find this substance to be markedly reduced in the bone marrow and blood of animals in which granulocytopenia has been produced by benzene.

Farley (20) reviewed from the literature thirty nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and malignant neutropenia, depending on whether the principle effect was on the granulopoietic, megakaryopoietic or erythroblastic tissues, or on all of these combined.

Madison and Squier were the first to incriminate amidopyrine, especially in combination with a barbiturate, as a cause of granulocytopenia. They found that the

onset of granulopenia was often directly preceded by the use of amidopyrine alone. Several of their patients were known to have a normal blood count and even a leukocytosis before the use of the drug.

Imerman and Imerman (34) in 1936 reported 8 cases of granulocytopenia developing from the use of dinitrophenol to reduce weight. All eight patients were women and their ages ranged from 18 to 48 years. The drug was used within apparently normal limits in every case. The most important pro-dromal symptoms occurred from ten days to four months after the drug was started and consisted of fever, sore throat and headache. Five of the patients recovered (the five who received pent-nucleotide therapy). The other patients, treated with adenine sulfate, liver extract and blood transfusions died.

Many other drugs have been mentioned, a few of which are antipyrine, acetanilid, atophan, phenacetin, novaldin, nirvanol, quinine, plasmochin and neostibosan. Amidopyrine, however, remains the chief offender and no more eloquent testimony can be given than the amazing decrease in the incidence of the disease not only in Denmark but also in the United States since the danger of the drug has been popularized. That amidopyrine is not the whole story is shown by incidents in which patients known to be suffering from granulocytopenia were given amidopyrine as a sedative with complete recovery following. (71)

In approximately one third of the cases of granulocytopenia, the blood culture is positive for some organism. This usually represents secondary infection, however, resulting from the depressed white count. The concept has been held by numerous authors that granulocytopenia is an infectious disease. (15, 21, 90, 93). Attempts to induce the disease by introducing into animals organisms isolated from lesions, bone marrow and blood stream of patients have failed to give any conclusive information. A large number of patients give a history of Vincent's angina prior to the clinical onset. This may well be the result of an unrecognized granulocytopenia of a chronic nature.

Fried and Dameshek (27) induced neutropenia experimentally by innoculating the blood stream of rabbits with the organism *Salmonella Suipestifer*. By grading the size of the dose they were able to produce two types of cases, those in which the animal recovered and fulminating cases ending fatally. The blood picture showed leukopenia and neutropenia but not a clear cut granulocytopenic picture.

Piersol and Steinfield (66) found that a long continued granulopenia could not be induced in healthy rabbits by the use of a small group of common bacteria.

A distinction should probably be made between marked secondary leukopenia and neutropenia due to an infection, and primary neutropenia in which the primary

lesion is in the blood or bone marrow and the organisms growing in a system devoid of granulocytes. If this distinction be kept in mind it would seem that it is attacking the etiology from the wrong standpoint to attempt to exhaust the bone marrow by the introduction of organisms.

In Dennis' experiments (16), various organisms derived from neutropenic patients were placed in parchment capsules and within the peritoneal cavity of animals to produce the condition. The animals having the most suggestive results showed on post-mortem examination, pneumococci, which were not among the bacteria tested.

Some very interesting work, the results of which have not yet been published, has been done by Lawrence (52) and his associates. They have produced in cats a disease similar to the human disorder and labelled "Infectious Feline Agranulocytosis". This has been shown to be due to a filterable virus and shows pronounced granulocytopenia on the sixth to ninth day after exposure. In the bone marrow there is invariably absence of differentiation into late myeloid forms at the height of the disease. The mechanism in both the human and the feline forms they feel may be due to peripheral destruction. The very sudden disappearance of neutrophils following amidopyrine would suggest this. In the cat a transfusion with one third a body volume of blood from another cat with the same quantity removed from the stricken animal by cardiac puncture was unable to elevate the white count and the granulocyte count- also suggesting peripheral destruction.

This theory that a filterable virus may be the cause of the granulocytopenic syndrome is extremely interesting and entirely plausible but would seem to await much more confirmation. Zikowski (94) in 1931 shared this view suggesting that a virus having a special affinity for granulopoietic tissue might induce a severe form of sepsis in the weakened organism, injuring not only the granulopoietic system but paralyzing the organ complex (liver, spleen and endocrine glands) which stimulate the bone marrow and govern the release of white cells into the blood stream.

A few authors believe that granulocytopenia may be a form of allergy in which the bone marrow is the area afflicted. Schilling (82), a name to be conjured with in blood picture interpretation, has this viewpoint. He was able to experimentally produce a blood picture similar to granulocytopenia by inducing anaphylaxis. Bromberg and Murphy (61) reported a case following prophylactic typhoid vaccination. Kracke reported a case and said; "The question of typhoid prophylaxis as a whole or partial cause of the condition must be considered." Meyer reported a case following malarial therapy. Those cases showing eosinophilia during an attack suggest anaphylaxis.

A rather interesting parallel is drawn by R.C. Beck (4) between granulocytopenia and pernicious anemia. Granulocytopenia in its recurrent phase is

somewhat similar in its clinical course to pernicious anemia.

Castle called attention to the intrinsic and extrinsic factors which are missing in pernicious anemia, and Beck postulates a chemotactic and maturation factor which may be missing in granulocytopenia. The marked therapeutic action of pentnucleotide extract may be due to these factors contained in it.

This concept is supported by the fact that there can be marked myeloid hyperplasia accompanying the neutropenia - in fact there can be any type of myeloid tissue. Beck's theory presupposes a chemotactic substance present in the broken down products of white cells (nucleic acid and its degradation products) which stimulates the bone marrow to myeloid activity. Thus stimulated, a maturation factor also present in the bone marrow comes into play. In a normal or hyperplastic bone marrow this second, maturation factor is assumed to be missing.

There is good evidence that diet may play a prominent part in the production of the syndrome. Miller and Rhoads (59) developed an ulcerative stomatitis in dogs by means of a diet causing blacktongue (Goldberger's diet). The terminal features of the illness were; I. Ulcerative, gangrenous stomatitis with spiral and fusiform organisms.



2. Leukopenia, granulopenia and a suppression of the hematopoietic elements of the bone marrow.

Lillie demonstrated lesions of the myelin sheaths of the nerves leading to the ulcerated areas - hence assuming the mucus membrane change to be trophic in nature. Total absence of granulocytes was never observed!

The bone marrow changes were: 1. A dilatation of capillaries. 2. A cessation of maturation of hematopoietic cells. These are the identical changes produced by the administration of certain toxic, aromatic compounds of the benzene series.

The relation between menstruation and the agranulocytic syndrome has been often noted. W.P. Thompsen (87) found that in 17 out of 18 young women with granulocytopenia, symptoms began within a day or two of menstruation. All were menstruating upon hospital admission. One or more recurrences were observed in six of these - each with the onset of catamenia. Two young women with previous attacks of granulocytopenia were followed through a menstrual period. In both a distinct but transient neutropenia developed with symptoms just before catamenia. The excretion of female sex and gonadotropic hormones was followed through the neutropenic phase of a well known male case of cyclic granulocytopenia. The results suggest that neutropenia occurs, in this young man, at the time of hormonal catamenia. (This patient developed within two years a diabetes insipidus - also interesting is the fact that they were able to abort

a scheduled attack with pentnucleotide extract. In this patient the fall in granulocytes definitely precedes the fever, buccal necrosis and other symptoms.)

A familial tendency to granulocutopenia is a possibility. Hart (32) suggested this having observed the syndrome in two sisters. Wolf (91) reported granulocytopenia as reactions to the same infection in brother and sister. Congenital granulopoietic insufficiency seems to exist in some cases but the granulopoietic tissue in most of the familial linked cases seems to have functioned normally for many years. Blumer dismissed the possibility of a congenital anomaly with this statement; "The same patient has reacted with the usual leukocytosis and granulocytosis to one attack of an infection and has shown a leukopenic and neutropenic reaction to another attack!" The possibility of a constitutionally limited bone marrow would seem as yet a theoretical question.

#### PATHOLOGY

The absence of white cells of the granulocytic series accounts for the high incidence of blood cultures, the anginal lesions and the peculiar form of inflammation which accompanies both benign and malignant granulocytopenia. Tissue ulceration and necrosis lack the exudative features of the normal reaction accompanied by polymorphonuclear leukocytic infiltration. Lymphocytes may be present, also macrophage cells and endothelial cells. Infection spreads like wildfire due to the lack of development of an inflammatory barrier. Any site in the body where bacteria

normally flourish may become the site of focal infection. This is particularly true of the gastro-intestinal tract. Ordinary inhabitants of this system may gain the ascendancy to become pathogenic.

Bone marrow infection may occur. Muller in his series of cases of influenza found that the red marrow had been invaded by organisms and damaged enough to interfere with granulopoiesis. The yellow marrow was not damaged and there was evidence to show that it had taken over some of the function of the red marrow. The bone marrow has never been shown to be infected in granulocytopenia save in the terminal stages of a septicemia but it would seem logical that this could occur - particularly in a fulminating case with an absence of granulocytes.

In fatal cases of granulocytopenia the bone marrow is degenerated to a very great extent. It varies in color from red to straw and may be liquified. Areas of patchy necrosis may be seen. The myelocytes and polymorphonuclear cells are absent or nearly so. Normoblasts and megakaryocytes are present in their normal numbers. With the maintenance of the gross, fatty structure, granulocytes may be absent or nearly so but erythrocytes, lymphocytes and endothelial leukocytes may be present. Generally the bone marrow is in a state of myeloid hypoplasia or aplasia. It may be normal as to myeloid elements and cases have been reported with a myeloid hyperplasia.

The condition of the spleen largely hinges on the septic or toxic processes that occur. Enlargement of the spleen, seen in some cases, is due to a tremendous increase in the reticulo-endothelial cells which outnumber the lymphoid cells. The splenic sinuses are filled with erythrocytes, reticulo-endothelial cells and lymphoid cells. Small anemic infarcts are occasionally seen.

The lymph follicles are small and atrophic and there are no lymphoblasts or young cells in the germinal centers, only mature lymphocytes. The cervical, sub-maxillary, peribronchial and mesenteric groups are frequently enlarged and may contain hemorrhages.

The liver is often enlarged and may show cloudy swelling. There is an increase in Kupffer's cells, bile pigment in the hepatic cells and bile casts in the capillaries. Sometimes there are interstitial lymphocytic infiltrations and there may be small, multiple foci of necrosis.

The lungs are frequently the site of a pneumonic process. The gross picture is similar to influenzal pneumonia. There is diffuse edema of a hemorrhagic type with no sign of inflammation and little phagocytosis. Sub pleural hemorrhages are frequently observed.

#### LABORATORY

Blood examination is, of course, extremely necessary both in the diagnosis of the condition and in

following the results of therapy. Blood counts should be made at the same hour every day for comparable results and preferably twice or three times per day. This takes cognizance of the leukocyte tides which occur daily.

The most outstanding laboratory finding is the leukopenia. In a severe case the total white cells may be so low as to be uncountable. In practically all cases the white count is below 2,000 and in some cases has been reported as low as 200. It may be necessary to use a 1:10 dilution of the blood rather than the usual 1:20.

The second most striking finding from a laboratory standpoint is the neutropenia. The morphology of the neutrophilic granulocytes is normal. There are no atypical cells, but their number is depleted to around 30 or 40 % in the chronic and less severe cases and there may be a complete absence in the fulminating cases.

Krumbhaar (48) recognized a terminal rise in the number of immature granulocytes in fatal cases of mustard gas poisoning. He labelled it "myelocytic crisis". Schilling (82) called this a "degenerative shift" and explained it on a disbalance between maturation and chemotactic factors. The supply of maturation factor having been depleted, the normally functioning chemotactic factor delivers immature myelocytes to the peripheral blood. This does not mean necessarily that the patient is recovering. It may be just an "agonal

outpouring" of the last of the young cells.

Eosinophiles may be either absent, present in normal quantities or in excess of the normal quantity. The same is true of basophiles.

The lymphocytes are, in most cases, greatly reduced. Their morphology remains perfectly normal. The mechanism of their reduction is obscure as there is no evidence of destruction of lymphoid tissue.

Monocytes and transitional cells become reduced in number as the disease becomes more severe. Their morphology remains normal. Ferrata (22) theorized that the macrophage cells of the reticulo-endothelial system might acquire granules and take over the work of the granulocytes in the emergency. He found such cells in the blood stream, containing either basophilic or eosinophilic granulations and termed them "hemohistiocytes".

If the disease lasts more than the usual ten days there may be a diminution of erythrocytes. In fulminating cases the erythrocytes are not affected because there is not time. When anemia is present it is usually of the secondary type with hypochromia.

In malignant granulocytopenia due to benzene or other drugs the blood platelets are reduced. In other forms of the disease they remain normal unless the bone marrow becomes aplastic.

Rutledge and his associates (78) found that during an attack the motility and viability of the granulocytes was much reduced, and their capacity to take the neutral red dye diminished. The motility never approached normal and their average length of life was only one-half normal.

Roberts and Kracke performed the following experiments to determine the toxicity of the serum. When their patient's white count totalled 400, they took 2 c.c. of the patient's blood (oxalated) and mixed it with 2 c.c. of normal blood of the same type. A normal control was set up. Differential and total white counts were made at two hour intervals for 48 hours but neutrophilic destruction could not be demonstrated. Other experiments have had similar results and one may say that sufficient proof is not at hand regarding the toxicity of serum in granulocytopenia.

Biopsy on the sternal marrow is the best method for differentiation between granulocytopenia with a maturation arrest and granulocytopenia with myeloid aplasia; and in aiding the differential diagnosis versus other bone marrow diseases. Biopsy on the fresh specimen of bone marrow is far superior to the specimen observed at autopsy.

The urine in granulocytopenia is not significant and the findings are those of any other febrile disease.

Many cases have a negative blood culture. When positive the organisms most frequently found are the streptococcus viridans and hemolyticus, the staphylococcus aureus, pneumococcus, colon bacillus and the bacillus pyocyaneus.

Cultures from the mouth and throat reveal the normal inhabitants of this area, Vincent's spirillum, the fusiform bacillus, pneumococci, streptococci and staphylococci. Their abundance is in direct ratio to the decline of granulocytes.

#### SYMPTOMS AND CLINICAL COURSE

There are two clinical types of the syndrome recognized, the acute, and the chronic or recurrent. In the former the onset is abrupt with a chill, high fever, and oftentimes a necrotizing angina. There may be extreme prostration, headache, vomiting, muscle pains and delirium suggesting sepsis. Jaundice and albuminuria are present in a certain percentage of cases. The blood shows an extreme degree of leukopenia and neutropenia. The ulceration and necrosis resembles diphtheria and may involve tonsils, pharynx, gums, tongue, larynx, esophagus and more rarely the skin, rectum, vulva, vagina or perineum. These ulcers are non-margined with overhanging edges and a complete absence of surrounding inflammatory zone. The lymph nodes of the neck are usually enlarged and the liver and spleen may or may not be palpable. Petechiae have been desc-



ribed in a few instances. The urine may show casts and bile. Signs of bronchopneumonia are prone to develop in the terminal stages of the disease.

The chronic, recurrent form of the disease may be relatively mild with symptoms of exhaustion or of a low grade infection. Patients with this type may have several attacks with weeks or months elapsing in between. This condition, with slight remissions, may persist for years or the patient may succumb during an acute exacerbation.

The presence of an ulcerative or exudative lesion in the throat or mouth should always suggest the necessity for a blood examination as well as a culture. The neutropenia precedes all symptoms according to the bulk of the literature on the subject. To wait for the appearance of sore throat, fever and angina is merely giving the army of organisms a chance to invade the tissues.

A typical history is the appearance of sore throat in a middle aged, usually debilitated individual, accompanied by chills and fever, ulceration and then membrane formation in the throat and on the buccal mucous membrane. If angina is absent, and few clinical signs are present, the diagnosis is far more difficult.

A total leukocyte and differential count should precede the extraction of teeth and tonsillectomy. If angina and fever are both absent and there are only

weakness, malaise and drowsiness, a frequent leukocyte and differential count should be made. Some authors state that normal numbers of circulating erythrocytes and thrombocytes are essential to the diagnosis and do not accept as granulocytopenia any case in which there is an absolute decrease in lymphocytes or endothelial leukocytes.

A sternal marrow biopsy would aid in the diagnosis and in distinguishing the aplastic from the hyperplastic type. Plum (68) has studied the bone marrow by puncture at various stages of the disease and states that the prodromal marrow shows a depression of immature granulocytes with normal mature cells. The fully developed condition is marked by absence of granulocytes and increase of myeloblasts. The beginning of regeneration is manifested by incipient production of granulocytes, increase in myeloblasts and pre-myelocytes but no adult granulocytes.

#### DIFFERENTIAL

Acute, follicular tonsillitis, Vincent's angina and diphtheria are to be differentiated by routine leukocyte and differential counts and appropriate clinical means. None of the afore-mentioned causes a leukopenia.

Patients with streptococcic sore throat with streptococcus hemolyticus septicemia usually have leukopenia but seldom less than 4,000 cells and the differential count usually shows at least 85 % neutrophiles. In typhoid cases and in influenza the leukocyte count is

rarely less than 4,000 and the neutrophilic percentage is at least 25. Generalized, rapidly advancing tuberculosis may show a marked, progressive leukopenia, as low as 3,000 cells, but the neutrophiles comprise from 90 to 99 %, mostly immature forms.

Pneumonia may at times cause leukopenia, rarely below 6,000 cells and there is always a preponderance of neutrophiles.

The condition known as lympho-sarcoma may cause leukopenia with a reduction in neutrophiles. Biopsy findings from the enlarged lymph glands will make this differentiation clear.

Aleukemic leukemia is characterized by an anemia and usually a thrombocytopenia. The anemia is marked, progressive and of a macrocytic type. In granulocytopenia, anemia is rare and of a microcytic type. In leukemia, blast forms appear eventually although they may not be present at the onset. Nucleated red cells are found and considerable bleeding from the gums occurs. The disease lasts a longer time than granulocytopenia.

In acute leukemia there is a very high cell count and there are large numbers of immature cells with the stem cells predominant. Acute leukemia is common in childhood and patients with a temperature of 102-4 degrees seem comparatively well. In granulocytopenia there is a very low cell count and very few stem cells and other young forms are present. Over 20 % of stem cells usually means leukemia. The syndrome of granulocytopenia is rare in childhood and temperatures of 102-4 degrees usually mean prostration. In lymphatic reactions

there is an absolute increase in lymphocytes which replace the neutrophiles to make the total leukocyte count normal or increased. There are usually many abnormal lymphoid cells, while in granulocytopenia the lymphoid cells are normal. Even so, the differential diagnosis is so difficult as to be well nigh impossible. The bone marrow biopsy will establish the diagnosis in doubtful cases. In the leukemias there is a crowding of the marrow with lymphoid cells.

Aplasia of the bone marrow (aplastic anemia) has anemia, thrombocytopenia and usually hemorrhagic pneumonia present. The disease is protracted and the bone marrow will often show a depletion of all its elements. There are sub-cutaneous hemorrhages from mucus membranes and other parts of the body. There is aplasia of the bone marrow as a whole. The yellow marrow is devoid of erythrocytes, leukocytes and megakaryocytes. There are leukopenia, neutropenia, thrombocytopenia and rapidly advancing hyperchromic anemia. There is a relative increase in lymphocytes and the color index is irregular. If anemia is present it is of the secondary type and the erythrocytes are more or less achromic.

Infectious mononucleosis usually occurs in young adults, often in their early twenties. Lymphadenopathy is often generalized, the spleen is palpable in many cases, leukocytosis is common, and the lymphocytes may show fenestration or vacuolization of their nuclei. The absolute number of neutrophiles is usually not re-

duced and many of them are immature. The injection of foreign protein will result in an increase in the number of circulating neutrophils. The clinical manifestations are usually much less severe than in granulocytopenia.

Care must be taken also to differentiate pernicious anemia in an aplastic phase and metastasis to the bones from neoplastic processes.

#### TREATMENT

All schools of thought agree that the primary step in therapy is to find the cause of injury to the bone marrow, if such cause can be isolated, and to remove it. History of the use of amidopyrine, dinitrophenol, gold salts, arsenicals, and numerous proprietary remedies should be especially sought for.

A review of the literature would suggest that most authors believe that a specific agent in therapy has not been found. The fact that some cases show spontaneous remission would make this rather hard to check. Never-the-less, there are numerous measures advocated and each has its enthusiastic supporters.

Friedemann (28), in 1927, advocated "stimulating" doses of x-rays. He applied one-twentieth of an erythema dose of roentgen rays to the bones of the skeleton giving from one to two treatments at intervals of from two to several days. He reported that improvement from this therapy may begin within from 24 to 48 hours, both as to clinical and blood picture. In the adult, the marrow in the long bones is mainly adipose tissue having little or no blood forming function. When pathologic demand exists

there is a formation of new centers by differentiation of the myeloblasts into granular myelocytes, the adipose tissue of the bone marrow being replaced by this newly formed tissue. One theory is that it aids in the formation of this new tissue. There is no evidence, however, that a cell is affected in any but a destructive way by the roentgen ray.

Doan's theory is that x-rays benefit those cases having a hyperplastic myeloid tissue. The rays bring about a destruction of this tissue with a liberation of autogenous nucleotide, which then initiates the maturation and delivery of granulocytes from the remaining myeloid foci.

It is definitely known, however, that the x-ray will bring about a reduction in the actual numbers of white cells of both granulocytic and lymphocytic patterns and the consensus of opinion seems to be that it might be a distinctly dangerous procedure by causing further bone marrow depletion.

The nucleic acid derivatives offer the most hope along the line of specific therapeutic measures. Reznikoff (71) introduced the use of intravenous adenine sulfate on the assumption that nucleic acid derivatives stimulate polymorphonuclear production. This is given in one gram doses, dissolved in 30 c.c. of saline brought to a boil. It is given as warm as the patient can stand as it goes out of solution easily. Thrombosis may occur

if some enters the wall of a vein and if it enters the surrounding tissues, necrosis and even sloughing may occur. Three doses for three days is usually adequate if the drug is effective.

In 1932, Jackson, Parker and Taylor (34) introduced pentnucleotide. They advocated the injection of 10 c.c. intra-muscularly four times a day if possible. Small doses of 1 c.c. are increased hourly until the above quantity is being given. An unpleasant reaction manifests itself by a sense of constriction in the chest, pounding in the head and general distress.

Jackson (36) was the first to demonstrate that pentose nucleotide existed in normal human blood. It is known to exist principally in the nuclei of living cells. Doan and his co-workers showed that granulocytes could be called from the marrow by the split products of nucleic acid, adenine and guanine, and there was no transitory leukopenia due to splenic storage. These substances, given intravenously to rabbits, caused a marked increase in the number of circulating granulocytes without affecting the other cells.

Doan, experimenting on normal rabbits with pentose nucleotide, produced not only an extensive degree of myeloid hyperplasia, but also an extra medullary myelopoiesis in the kidneys and spleen.

The nucleoproteins of the body exist as combinations of nucleic acid with protein material. The acid

is found within the cell in free form in cases. The amount and character of the protein with which the free acid combines is variable. Those tissues which contain the largest amount of nuclear material are richest in nucleic acid. This includes such tissues as thymus, spleen, liver and hematopoietic tissue. Nucleic acids on hydrolysis yield the purine and pyrimidine nucleotides. The purine nucleotides on hydrolysis yield the purine bases, adenine and guanine.

Jackson and associates (35) in their series of cases used the unbroken pentose nucleotide K-96 under the direction of Harvard Medical School. Twenty patients were treated. Of the thirteen whose condition could be classed as malignant, seven recovered. The first sign of improvement occurred on the fifth day usually. The consistency of this they compared with the reticulocyte raise which occurs in pernicious anemia following liver therapy. Jackson and his workers concluded: "We believe that these nucleotides may have a definitely favorable effect on the very active bone marrow and in certain cases we believe the substance well worth trial."

Gordon (29) has classified the types of treatment which have been employed in granulocytopenia;

A. Blood - intravenous, intramuscular and intraperitoneally - both healthy and that from a recovered case.

B. Biological - nucleinic acid, nucleotide, leukocytic cream, bone marrow, sterile milk and foreign proteins.



C. Bacteriological - typhoid vaccine, bacteriophage and bacterial serums.

D. Glandular - mainly from the liver, fetal spleen, thyroid and adrenals.

E. Physical - x-rays, radium and sterile abscesses.

F. Chemical - adenine sulfate, purine base, calcium sulfate, arsphenamine.

G. General - allied stimulation, intravenous glucose, intravenous saline, diet and locally mouth washes, irrigations, oral hygiene.

Gordon's successful treatment is as follows:

1. A high nuclein diet.
2. General therapy as mentioned above.
3. Small blood transfusions - (contra-indicated where there are signs of liver exhaustion such as jaundice as an increased strain on the liver will cause blood to be broken down.)
4. 40 c.c. of whole blood intramuscularly twice a day.
5. Nucleotide and nucleinic acid.

We have seen that diet may play a very important role in the etiology of this condition. If this be true, it should follow that it might also prove important in therapy. Doan was able to reduce the red marrow of the radius of pigeons to an extreme hypoplasia by underfeeding.

The work of Miller and Rhoades (59) in the production of acute stomatitis with neutropenia and granulocytopenia in dogs by means of a black tongue diet would strongly suggest that a diet rich in vitamin B should be

of material aid.

In granulocytopenia due to arsphenamine very good results have been had from the intravenous use of sodium thiosulfate. This can also be given by mouth. McBride and Dennie suggested that it be given in not more than 20 c.c. of distilled water, with daily intravenous injections for four days, and then on alternate days, for as many injections as may be necessary, in doses starting with .3 gram and increasing by .15 gram daily. This drug is non-toxic in quantities up to 2 grams. The prodromal signs of toxicity are itching and a mild rash, prolonged fever and a tendency toward purpura..

Splenectomy has been advocated in this condition and has been tried. It is generally conceded, however, that the procedure is poorly suited to the form of pathology present in these cases.

Transfusions have been used in many of the cases reported, some recovering and some dying. Reports, on the whole, have been satisfactory although the procedure is essentially empirical. There is no evidence that transfusions stimulate the neutrophilic development, and the number of neutrophiles added in 500 c.c. of blood would be of little assistance, particularly as the life of a neutrophile is short (5 days). There is a possibility that blood from a healthy donor might have the principles to bring about normal maturation but here again it is highly conjectural and the amount would be small.

Reznikoff (7I) feels that fatigue is a definite factor in the production of the syndrome. He reasons that treatment should include absolute rest and freedom from worry as far as possible. The chronic cases in particular improve with rest.

Reznikoff has a theory regarding the action of liver, quite actively used in therapy. He states that the myeloid elements of the bone marrow are in close contiguity with the hyperplastic, erythroblastic tissue and may be influenced by changes in the latter. With response to liver therapy the leukocytes usually increase (in pernicious anemia anyway) and with this in view many workers have been giving intravenous liver extract for acute granulocytopenia. Many favorable reports have been given.

Miscellaneous agents which have been given include turpentine to produce a local abscess, intramuscular injections of milk, intravenous injections of gentian violet and acriflavine; all have been used to stimulate the production of granulocytes, but to no avail. Leukocytic cream, typhoid vaccine, bacteriophage and bacterial serums have all been used. Glandular extracts include those from thyroid, adrenals, spleen, liver. Other recommended measures have been elsewhere mentioned.

General measures include treatment of the oral lesions. Sodium perborate gargles followed by swabbing of the ulcers with a two percent solution of copper sulfate should be used five times per day.

Foci of infection should be cleared up with particular reference to the oral cavity. Surgery should be undertaken if absolutely necessary. Abscesses should be localized and drained just as with a normal blood count.

A diet rich in vitamin "B" complex seems to have value, especially in the chronic cases.

Fluids should be forced. Some authorities recommend giving as high as five or six quarts per day.

It might be well to mention here one recent therapeutic measure which has been used by Griffin and Watkins of the Mayo clinic with good results. This is extract of yellow bone marrow. The dosage is 20-30 grams daily during the acute stages. This type of therapy is said to produce a response in 24 to 48 hours, whereas pentnucleotide therapy takes from four to five days. This bone marrow is given orally and does not produce the severe, painful reactions of pentnucleotide.

While no one therapeutic measure may be hailed as specific, the enthusiastic endorsement given a few of the above mentioned measures would certainly seem to merit their further study.

#### THE RELATIONSHIP OF GRANULOCYTOPENIA TO THE SULFONAMIDE DERIVATIVES

Since the middle of the last decade, a new era in Medicine has arisen. Labelled the age of chemo-

therapy, enthusiasm has centered around one group of drugs; those of the sulfonamide series. Variously known as the "magic drugs", and the "wonder drugs", their use has become universal and their efficacy proven for all time. Unfortunately, they are not without their dangers, dangers bound to be magnified through the promiscuous use - and misuse which always follows in the wake of such a discovery. One of the graver complications of the use of these drugs is the development of granulocytopenia. The complication is particularly sinister in that the toxic effects may occur days after cessation of the drug, and relatively few clinical manifestations occur until the syndrome is definitely established. Reznikoff (71) predicts that the sulfonamide derivatives will replace amidopyrine as the number one cause of granulocytopenia.

To illustrate the type of granulocytopenic syndrome which follows on the heels of sulfonamide therapy, its method of induction, time of onset, outcome, and some therapeutic measures which have been used to combat it; I have deemed it wise to select at random some case histories from the current literature. Many of these have points in common, but in general there are enough variable features that one hesitates to predict the action of the drug in any given set of circumstances. This unpredictability remains the great mystery of granulocytopenia. Why the sulfonamide drugs should aid the white cells in one person and deplete them in another is beyond the scope of our present knowledge.

Schwartz, Garwin and Koletsky (83) report a case of fatal granulocytopenia following sulfanilamide therapy. The case, a chronic, penile ulcer.

The treatment consisted of 5 grams of sulfanilamide for two days, then two grams daily for three days. A routine blood count at this time showed total leukocytes to be in the neighborhood of 2,000. The drug was stopped at the end of 21 days when the patient had received a total of 56.6 grams. Four days later the patient was icteric with the liver well below the costal margin. There was slight necrotic ulceration in the tonsillar region. Death occurred on the following day. The necropsy included a myeloid series of the bone marrow which showed maturation arrest with stem cell hyperplasia and complete absence of more mature cells.

Berg and Holtzmann (5) report the case of a man, age 22, in excellent health, who received sulfanilamide therapy for gonorrhea.

Five grains were given every four hours for five days at which time the patient developed slight fever, cramps and nausea. The sulfanilamide was stopped altogether, to be started four days later. After ingestion of a total of 38 grams he had a chill, fever, uncontrollable vomiting and abdominal pain. The diastolic blood pressure was 50, pulse 130, temperature 107 degrees. A blood count revealed a total absence of polymorphonuclear cells. Death occurred in spite of pentnucleotide therapy.

F.D. Johnston (40) reported a case in a woman, age 23, who was treated for a puerperal infection due to the hemolytic streptococcus, group A. 61.3 grams of prontosil was given both orally and intravenously over a 20 day period. A blood count at this time showed a total white count of 1500 with no granulocytes and a severe secondary anemia. Therapy for the granulocytopenia consisted of a drip transfusion of defibrinated blood given over a 28 hour period. Pentnucleotide injections were given twice daily for 5 days (.35 g.). The patient was well two weeks later with a white count of 7550 - normal differential.

Johnson also reported a case which followed the treatment of acute pemphigus with M. and B. 693.

The patient, a male age 29, was admitted to the hospital in profound toxemia with a temperature of 103 degrees, pulse of 116, respirations 20. There were inch wide lesions covering the entire body. These lesions were bullae filled with clear fluid. The response to M. and B. 693 was dramatic after only 38 grams of the drug had been given, but the patient had a white count of 6000, with only 17 % polymorphs., of which 90 % were immature. Pentnucleotide therapy was started and the blood picture rapidly became normal.

Sakula reports (81) the treatment of a case of meningitis due to the Pfeiffer bacillus with M. and B. 693, which was complicated by granulocytopenia.

The patient, age  $2\frac{1}{2}$  years, was admitted to the

hospital with a temperature of 103 degrees, pulse 128, respirations 48. Neurological signs were positive for meningitis. Culture of the spinal fluid proved Hemophilus Influenzae. 2.5 grams of M and B 693 were given per day. When 17 grams had been given the drug was stopped due to a generalized rubella rash all over trunk and limbs. The white count was 23,000 with 79 % neutrophils. By the next day the rash was gone. Five days later the temperature and pulse, which had been normal, rose again and the drug was again given in doses of 2 grams per day for 5 days. At the end of the five days the leukocyte count had fallen to 2,100 with 5 % neutrophils. Pentnucleotide was given for 9 days at the end of which time the white count was 15,500 with 58 % granulocytes.

J.G.G. Borst has reported (8) a case of death resulting from an agranulocytic complication of treatment with prontosil flavum.

The patient, age 61, was admitted to the hospital with a temperature of 102 degrees, white count of 8,000 with 51 % polymorphs. The diagnosis was pyelocystitis. For ten days she received 6 tablets per day of prontosil flavum (300 mg. per tablet). Her symptoms disappeared, the temperature dropped and the urine became pus and bacillus free. prontosil was stopped and the pyelocystitis returned. Prontosil was resumed at the same dosage for 20 more days. A routine white count at this time



showed a total of 1225 with  $2\frac{1}{2}$  % polymorphs. Two days later the patient's throat was red, swallowing was difficult and death ensued. The white count at the time of death was 960 with 1 % polymorphs., 87 % lymphocytes and 12 % monocytes. (Prontosil flavum is usually given to patients suffering from acute streptococcal sepsis and where the illness is already severe, slight symptoms of intoxication are not recognized easily so that not even a serious complication like granulocytopenia will alter the picture radically enough to attract attention. The importance of routine blood counts is again emphasized.)

Jennings and Southwell-Sander report (39) a case developing in a housewife, age 39, with a diagnosis of ulcerative colitis with stool culture positive for dysentery bacilli.

Sulfanilamide, four grams per day, was given for three weeks. The infection disappeared and the patient was discharged as well. Five days after quitting the drug, there was a temperature of 103.5 degrees. The pharynx was reddened with a white exudate. The total white count was 444 with a complete absence of granulocytes. The treatment consisted of pentnucleotide, .7 gram intramuscularly twice a day for 3 days then once per day for 2 days. The temperature became normal in 2 days. The white count returned to normal in one week.

Long, Haviland, Edwards and Bliss (56) have given an excellent analysis of the toxic manifestations of sulfanilamide and its derivatives. They have analyzed the incidence and types of toxic reactions occurring in hospitalized results, 1,000 of whom were treated with sulfanilamide, 297 with sulfapyridine and 291 with sulfathiazole in Johns Hopkin's hospital over a period of years.

They conclude that leukopenia with granulopenia may occur early or late in the course of therapy with sulfanilamide or its derivatives. They have noted a sharp drop in total leukocytes in certain cases following a single dose, in other cases not showing up until 60 or 70 days after treatment. No deaths have been reported from disturbances of the white cells during the first 12 days of therapy.

They state further that acute granulocytopenia is a rare occurrence and the most common time of appearance is from the 17th to the 25th day. Hence the blood count should be checked daily from the 12th day on. Stop the drug and vigorously force fluids in any decrease of total white cells and polymorphs. The forcing of fluids helps to rid the body of the drug. Transfusions are to be used when the hemoglobin value falls below 70 %. The prognosis is good when the toxic reaction is recognized in its inception.

At the time of visit to one of these patients, the

physician should inquire as to his symptoms - especially in respect to headache, body aching and malaise. These are often the precursors of many of the toxic reactions to sulfanilamide or its derivatives. The sclera should be examined for jaundice, the mucus membranes for pallor and the skin for evidences of rash. The temperature should always be taken in order to detect whether drug fever is present.

Lastly, one should remember that if a patient has once had a toxic reaction with one of these drugs, the next time the therapy is instituted he is likely to have an earlier and more severe reaction. Patients having a toxic reaction to one of these drugs may have a similar reaction when another of the group is prescribed.

The following table shows the incidence of granulocytopenia which they found in this series.

<u>SULFANILAMIDE</u>	<u>SULFAPYRIDINE</u>	<u>SULFATHIAZOLE</u>
in .1 % of cases;	in .3 % of cases;	not reported
occurs on 14th to	14th to 40th day,	but may occur.
40th day, more frequent on 17th to 25th.	17th to 25th mostly.	

#### PROGNOSIS

The prognosis in granulocytopenia is always grave, the mortality being at least 75 %. The outlook appears to be more serious with severe grades of leukopenia and complete absence of polymorphonuclear cells from the blood, though even these cases may recover. Total monocytes numbering 100 to 200 are believed to be of favor-

able import. The appearance of eosinophiles, a progressive rise in the white count and in the number of granulocytes are good omens. In general the outlook will depend upon the kind and degree of bone marrow injury, the degree of secondary infection and the general recuperative power of the marrow.

#### SUMMARY

1. Granulocytopenia is a syndrome characterized by an acute, febrile course, neutropenia, ulcerative lesions of the mucus membranes, and a high mortality.

2. Although probably existing prior to 1922, we usually date it from Schultz' observations in that year. Our concept of the disease has changed gradually as it has become apparent that a large number of bacterial, toxic, chemical and physical agents can produce it. The group of cases designated "idiopathic" is becoming steadily smaller as more of these agents are discovered.

3. The term "agranulocytic angina", in greater use than any other, is somewhat ambiguous, as are many other of the suggested names. The term "granulocytopenia" is brief, descriptive, and contains no ambiguities.

4. Perhaps the most outstanding work in establishing the etiology of the condition was that of Kracke, who incriminated drugs containing the benzene nucleus. Many other drugs, not containing this radical, have been shown to produce the syndrome; as well as bacteria, physical agents, sera and antitoxins. A congenital condition of the bone marrow has been demonstrated in some cases. Allergy has been found closely associated in some cases.

A close relationship to the menses and pregnancy has long been noted. Dietary factors and the possibility of a virus cause have recently been mentioned in the literature.

5. The most striking pathological finding is the total or relative absence of white cells of the granulocytic series in both bone marrow and the peripheral circulation. The bone marrow at autopsy may be normal, hypoplastic or hyperplastic. Most of the other pathology is secondary, contingent upon the reduced leukocytic defenses of the body.

6. Diagnosis of the condition is fairly easy provided frequent blood examinations are made. Leukopenia and extreme neutropenia are the outstanding findings. Differential diagnosis versus aleukemic leukemia and other rare blood diseases is difficult but possible by a strict analysis of the blood picture and the clinical findings. The presence of an ulcerative lesion in the mouth or throat should always suggest the necessity for a blood examination.

The primary step in therapy is to find the cause of injury to the bone marrow and remove it. No specific has been discovered for the condition although many have been suggested and tried. The most promising of these are the nucleic acid derivatives, adenine sulfate and bone marrow extract. Supportive measures include frequent transfusions, removal of foci of infection and treatment of the local lesions. Due to the tendency toward spontaneous recovery, the results of

any therapy are difficult to evaluate.

8. Granulocytopenia can be definitely caused by drugs of the sulphonamide series. Several case histories and the results of a series of 1,588 cases upon which records were kept at Johns Hopkins hospital are presented to illustrate this. The extremely common useage of these drugs make this complication an important consideration, particularly as the granulocytopenia may be latent, arising days after the drug has been discontinued. Blood examination should be done frequently during the course of therapy with these drugs. Failure to do this is almost criminal negligence.

9. The prognosis is extremely grave in granulocytopenia resulting from any cause whatsoever. Drugs known to cause the condition should be avoided wherever possible. Drugs in common use by the laity should be labelled as to contents, and the public should be instructed to avoid pain relieving or soporific drugs about which they have no knowledge. These precautions, accompanied by frequent and thorough blood examinations upon the part of the physician, should do much toward reducing the incidence of this bizarre and lethal syndrome.

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